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Sleep deficits in mild cognitive impairment are related to increased levels of plasma amyloid-β and cortical thinning

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ABSTRACT

Evidence suggests that amyloid-beta (Aβ) depositions parallel sleep deficits in Alzheimer's disease (AD). However, it remains unknown whether impaired sleep and changes in plasma Aβ levels are related in amnestic mild cognitive impairment (aMCI) subjects, and whether both markers are further associated with cortical thinning in canonical AD regions. To jointly address this issue, we investigated relationships between changes in physiological sleep and plasma Aβ concentrations in 21 healthy old (HO) adults and 21 aMCI subjects, and further assessed whether these two factors were associated with cortical loss in each group. aMCI, but not HO subjects, showed significant relationships between disrupted slow-wave sleep (SWS) and increased plasma levels of $A\beta_{42}$. We also found that shortened rapid-eye movement (REM) sleep in aMCI correlated with thinning of the posterior cingulate, precuneus, and postcentral gyrus; whereas higher levels of $A\beta_{40}$ and $A\beta_{42}$ accounted for grey matter (GM) loss of posterior cingulate and entorhinal cortex, respectively. These results support preliminary relationships between Aβ burden and altered sleep physiology observed in animal models of AD amyloidosis, and provide precise cortical correlates of these changes in older adults with aMCI. Taken together, these findings open new research avenues on the combined role of sleep, peripheral Aβ levels and cortical integrity in tracking the progression from normal aging to early neurodegeneration.

Introduction

The aggregation of Aβ into toxic oligomers plays a central role in the pathogenesis of Alzheimer's disease (AD), the most common cause of long-term institutionalization in persons over 65 in developing countries (Reitz et al., 2011). $A\beta_{40}$ and $A\beta_{42}$ isoforms are the major constituents of amyloid plaques, $A\beta_{40}$ being the most common and $A\beta_{42}$ more fibrillogenic and prone to pathological states (Burdick et al., 1992; Iwatsubo et al., 1994). According to the amyloid cascade hypothesis, accumulation of extraneuronal Aβ deposits results in neuronal death and synaptic failures that impair cognitive function and ultimately may lead to AD (Hardy and Selkoe, 2002). Although mechanisms of Aβ-related cognitive deficits have been extensively studied (Cleary et al., 2005; Shankar et al., 2008; Stephan et al., 2001), the impact of Aβ burden on non-cognitive symptoms of AD is unknown to date.

Sleep disturbances are one of the most troubling symptoms during progression of AD (Loewenstein et al., 1982; Prinz et al., 1982; Vitiello et al., 1990). Recent studies have revealed a link between the presence of Aβ plaques and the occurrence of sleep disturbances in a mouse model of AD amyloidosis. More specifically, disrupted sleep patterns emerged after early deposition of Aβ plaques in the hippocampus of APP-PS1 mice and reversed after active immunization with $A\beta_{42}$ (Roh et al., 2012). However, it remains to be determined whether association between impaired sleep and Aβ load is extended to humans, and more precisely to early stages of neurodegeneration.

Growing evidence suggests that sleep disturbances begin years before the clinical onset of AD (Geda et al., 2004; Hita-Yañez et al., 2012; Lee et al., 2008; Westerberg et al., 2012). Accordingly, we have recently found that aMCI subjects, older adults at higher risk for AD (Petersen et al., 1999), showed reduced REM sleep and disrupted SWS (Hita-Yañez et al., 2012) together with a higher prevalence of self-reported sleep problems and sleep onset misperception when compared to HO adults (Hita-Yañez et al., 2013). MCI subjects also show significant changes in plasma Aβ levels (Mayeux et al., 2003; Schupf et al., 2008; van Oijen et al., 2006) in addition to AD lesions, confirmed histopathologically, in cingulate and parieto-temporal cortical structures (Driscoll et al., 2009; Hänggi et al., 2011; Whitwell et al., 2007). However, it remains unknown if sleep disturbances and plasma Aβ levels observed in MCI subjects are associated with loss of cortical integrity in these canonical AD regions.

To jointly address this issue, we first determined whether plasma Aβ levels are related to changes in sleep physiology and/or cortical thinning in aMCI subjects. Second, we investigated if sleep deficits and/or increased Aβ levels reported in aMCI subjects accounted for patterns of cortical loss characteristic of incipient neurodegeneration.

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Material and methods

Subjects

Twenty-one older adults with aMCI (6 females, mean age: 69.8 ± 6.4 yr) and 21 HO subjects (10 females, mean age: 66.9 ± 5.5 yr) were enrolled in the study. Participants were primarily recruited from older people's associations, normal community health screening, and hospital outpatient services. All of them gave informed consent prior to experiments. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Pablo de Olavide University. Here, we used the same sample employed in a previous study (Hita-Yañez et al., 2012) with the exception of 8 subjects who were excluded due to lack of plasma samples and/or cerebral magnetic resonance imaging (MRI). Each participant underwent structured, uniform evaluation that included a medical history, neurological examination, and cognitive function testing. Only those who met criteria for HO or aMCI status (see below) were included in the study.

aMCI subjects showed an idiopathic amnestic disorder with absence of impairment in cognitive areas other than memory as revealed by neuropsychological testing; they further met the diagnostic criteria of aMCI proposed by Petersen et al. (1999): (i) subjective memory complaints corroborated by the informant; (ii) objective memory loss confirmed by the Spanish version of the Logical Memory subtest extracted from the Wechsler Memory Scale-Third Edition (Wechsler, 2004) (scorings 1.5 standard deviations below the age-appropriate mean); (iii) global score of 0.5 (questionable dementia) in the clinical dementia rating (CDR) (Hughes et al., 1982); (iv) normal independence function, judged both clinically and by means of the interview for deterioration in daily living activities validated in the Spanish population (Böhm et al., 1998); and (v) no DSM-IV criteria for dementia. The global cognitive status was assessed by the Spanish version of the Mini Mental State Examination (MMSE) (Lobo et al., 1979). Depression was excluded with the shorter version of the Geriatric Depression Scale (Yesavage et al., 1983). Inclusion criteria for HO subjects were (i) absence of cognitive impairment (memory, language, attention, and executive function) confirmed by neuropsychological testing; (ii) CDR global score of 0 (no dementia); and (iii) normal independent function. Depression symptoms were excluded by using the same criteria as for aMCI subjects. HO and aMCI subjects were tested with the same neuropsychological battery.

Cerebral MRI was previously examined in all participants to rule out lesions such as territorial cerebral infarction, brain tumor, hippocampal sclerosis, and/or vascular malformations. Those participants with large periventricular and/or deep white matter lesions, revealed by scores ≥2 on the Fazekas ischemic scale (Fazekas et al., 1987), were excluded from the study. Subjects reporting a history of neurological, psychiatric disorders, and/or major medical illness (chronic renal, hepatic, pulmonary or endocrine) were not allowed to participate.

The absence of secondary causes of cognitive deficits was confirmed by laboratory tests including complete blood count, blood chemistry, vitamin B12/folate, and thyroid function tests. None of the participants were taking cholinesterase inhibitors and/or medication affecting the sleep-wake cycle (benzodiazepines, tricyclic and/or serotonin reuptake inhibitors) at the time of recruiting or during the study. Neither did they report sleep-disordered breathing, movement disorders during sleep nor unusual sleep schedules (e.g., shift work), which was corroborated by their bed partners and/or caregivers. Individual scores of the Epworth Sleepiness Scale (ESS) were below the cut off for suspected sleep disorders associated with excessive daytime sleepiness (Johns, 1991).

Plasma Aβ levels

Venous blood samples were obtained after overnight fasting. Blood samples were collected in 10 mL K2-ethylenediaminetetraacetic acid (EDTA) coated tubes (BD Diagnostics), and further centrifuged (3500 rpm) at 4 °C for 5 min. Supernatant plasma was collected and aliquoted into 250-μL polypropylene tubes containing 8.32 μL of a protease inhibitor cocktail (cOmplete Ultra Tablets mini, Roche). Plasma samples were stored at −80 ºC and thawed immediately before assay.

Plasma Aβ levels were measured blind to cognitive status in duplicate samples (50 μL) according to manufacturer's instructions (Invitrogen). Averaged values (pg/ml) were used for statistical analyses. Human $A\beta_{40}$ and ultra sensitive $A\beta_{42}$ specific enzyme-linked immunoassay (ELISA) kits were used for this purpose. The detection limit of these assays was 0.52 pg/ml for $A\beta_{40}$ and 0.27 pg/ml for $A\beta_{42}$. Both inter-assay and intra-assay coefficients of variation were below 10%. The $A\beta_{42}/A\beta_{40}$ ratio was additionally computed for each subject given its ability to identify cognitively normal subjects who later converted to MCI or AD (Graff-Radford et al., 2007).

Polysomnographic sleep recordings

The polysomnographic (PSG) protocol included electroencephalographic (EEG) recordings, vertical and horizontal electrooculography, and electromyography of submental muscles. Electrophysiological recordings were performed with gold cup, 10 mm diameter electrodes (Grass, USA) filled with electrolytic cream, and attached with surgical tape (face placements) and collodion (scalp placements). Overnight PSG recordings were performed in a sound-attenuated bedroom with infrared video-controlled supervision.

PSG recordings were amplified (BrainAmp MR, Brain Products, Germany), filtered (0.1–100 Hz bandpass), digitized (250 Hz, 16-bit resolution), and stored in digital format for subsequent analyses. Scoring of sleep stages was performed by a trained technician, blind to the study purpose, following standard criteria (Rechtschaffen and Kales, 1968). Criteria for scoring EEG arousals were taken from the American Sleep Disorders Association report (American Sleep Disorder Association, 1992); the level of sleep fragmentation was determined by computing the arousal index in each sleep stage. This index resulted from dividing the number of arousals in a sleep stage by the time (in hours) spent in that sleep stage. Only those PSG parameters that showed significant group differences between HO and aMCI subjects (Hita-Yañez et al., 2012) were correlated with plasma Aβ levels and cortical thickness in each group.

Cerebral MRI acquisition, image preprocessing and cortical thickness estimation

Cerebral images were acquired on a whole-body Philips Achieva 3 T MRI scanner equipped with an 8-channel head coil. A high-resolution MP-RAGE (magnetization-prepared rapid gradient echo) T1-weighted cerebral scan was obtained from each participant. Acquisition parameters were empirically optimized for grey/white matter contrast (repetition-time = 2300 ms, echo-time = 4.5 ms, flip angle = 8°, matrix dimensions 320 × 320, 0.8 isotropic voxel, no gap between slices, time per acquisition = 9.1 min).

Measurements of cortical thickness were obtained with Freesurfer v5.1 (http://surfer.nmr.mgh.harvard.edu/) following standardized analysis protocols. Briefly, individual brain scans were reoriented, normalized for intensities, and resampled to 1-mm isotropic voxels. Skull stripping was automatically performed for each previously normalized brain volume using a hybrid approach that combines watershed algorithms and a deformable surface (Segonne et al., 2004). To obtain individual cortical surfaces, we applied a semi-automated procedure that includes i) segmentation of the white matter, ii) tessellation of the grey/white matter boundaries, iii) inflation of the cortical surface, and iv) automatic correction of topological defects (Dale et al., 1999). Removal of non-brain tissues was manually performed in each participant. Next, cortical surfaces were automatically constrained to a spherical topology (Fischl et al., 2001) for which parameterization,

surface registration and bases were previously provided (Fischl et al., 1999a; Van Essen et al., 1998). Pial/white matter boundaries were manually enhanced on a slice-by-slice basis in each participant to increase the reliability of cortical thickness measurements. Special attention was paid to cortical regions at the border with cerebrospinal fluid (CSF) in order to avoid partial volume effects.

Thickness measurements were obtained from the individual reconstructed cortical surfaces with submillimeter accuracy. Cortical thickness at each vertex was defined as the average of the shortest distance between vertices of the grey/white matter boundary and the pial surface computed in both directions (Fischl and Dale, 2000). Individual thickness maps were further transformed into the same spherical coordinate system of cortical surfaces, and then resampled to the average spherical surface by aligning each individual cortical folding pattern to the average folding pattern of the entire population. This procedure has demonstrated enhancement of localization of cortical features among participants, minimizing metric distortions (Fischl et al., 1999b). Methods employed here for the measurement of cortical thickness have previously been validated against histological data (Rosas et al., 2002) and manual segmentation (Kuperberg et al., 2003; Salat et al., 2004). Cortical thickness maps were finally smoothed using non-linear spherical wavelet-based denoising schemes, which have previously demonstrated enhanced specificity and sensitivity at detecting local and global changes in cortical thickness (Bernal-Rusiel et al., 2008).

Spatial filters based on non-linear spherical wavelets depend on three parameters: i) the oscillation factor, which controls the shape of the filter; ii) the dilation factor, which correspond to the extent of the spatial smoothing (this value is not equivalent to the full width at half maximum value of the Gaussian kernel); and iii) the number of the finest decomposition levels at which the thresholding is applied. Based on previous studies (Bernal-Rusiel et al., 2008), we applied an oscillation factor of 1 and a threshold-finest level of 1 because these values have obtained the best results in cortical thickness analyses. By applying sequential statistical thresholding based on a previously validated hierarchical model (Bernal-Rusiel et al., 2010), we further determined that the optimal extent of the smoothing (dilation factor) fluctuated from 3 to 11, depending on the statistical contrast.

All analyses were performed in Dell™ T7400 workstations, (4 Intel Xeon™ Dual Core processors, 3.2 GHz each, 32 GB RAM) with MATLAB® v. 7.9 running on Linux Centos4 X86-64 bits.

Statistical analyses

We previously assessed the normality assumption of our data by using the Kolmogorov-Smirnov test. All demographics, cognitive scores, sleep parameters and plasma Aβ values were normally distributed, allowing us to apply parametric statistical tests.

Group differences in demographic and cognitive variables were assessed with unpaired t-tests, whereas the influence of gender was tested with the chi-square test due to the categorical nature of this variable. Group differences in PSG sleep parameters and plasma Aβ levels ($A\beta_{40}$, $A\beta_{42}$, $A\beta_{42}/A\beta_{40}$ ratio) were assessed by a multivariate analysis of covariance (MANCOVA), adjusted for age and gender. Next, linear regression analyses were conducted to determine if group differences in PSG sleep were significantly associated with changes in plasma Aβ levels. If at least one of the two groups reached significant correlations, differences between regression slopes were further assessed. All regression analyses were also adjusted for age and gender. These statistical analyses were performed with SPSS v. 15 (SPSS Inc., Chicago, IL).

Group differences in cortical thickness between HO and aMCI subjects were assessed for the original (21 subjects per group) and for a smaller sample matched in age and gender (16 subjects per group). By using a hierarchical statistical model (Bernal-Rusiel et al., 2010), we performed an analysis of covariance (ANCOVA) for each hemisphere including group as the main factor (HO and aMCI), and age, gender, and normalized mean cortical thickness as covariates. The significance threshold was set at $P < 0.05$ after correcting for multiple comparisons, with a cluster extent threshold of 90 vertices.

Relationships between cortical thickness and sleep deficits (i.e., REM percentage and density of SWS arousals) or plasma Aβ levels ($A\beta_{40}$, $A\beta_{42}$, $A\beta_{42}/A\beta_{40}$ ratio) were assessed in each hemisphere for HO and aMCI subjects separately, by using linear regression analyses adjusted for age, gender and normalized mean cortical thickness (corrected for multiple comparisons, $P < 0.05$; cluster extend threshold >90 vertices). If at least one of the two groups showed significant correlations, we then assessed group differences between regression slopes. To further determine the influence of plasma Aβ levels on the above relationship, we separately included Aβ markers that reached significance as nuisance variable in the general statistical model. Likewise, we investigated relationships between plasma Aβ levels and changes in cortical thickness by removing effects of significant sleep deficits (i.e., REM percentage and density of SWS arousals).

Statistical relationships between cortical thickness and changes in either sleep or significant Aβ markers were assessed using a hierarchical statistical model. This methodology aims at controlling erroneous detections in two sequential steps: firstly, at the cluster level, over smoothed statistical maps via random field theory; and secondly at the vertex level, over unsmoothed statistical maps by applying an adaptive false discovery rate procedure to clusters previously detected. The superior performance of this methodology over other statistical approaches has previously been confirmed in simulation studies, and further validated in a cross-sectional experiment comparing moderate AD patients with HO subjects (Bernal-Rusiel et al., 2010).

Results

Demographic and cognitive profile

Both groups were statistically similar in age, gender and years of education. As expected, they differed in global cognitive status and memory function (Table 1). In particular, aMCI showed lower MMSE scores ($P = 0.01$), impaired immediate ($P = 3 \times 10^{-6}$) and delayed recall ($P = 5 \times 10^{-9}$) compared to HO subjects.

Plasma Aβ levels

Table 2 shows mean values of plasma Aβ levels in HO and aMCI. Overall, plasma Aβ levels differed between the two groups ($F_{3,36} = 4.41$, $P = 0.01$). Univariate analyses revealed that aMCI subjects showed significantly higher concentrations of $A\beta_{40}$ ($P = 0.006$) and $A\beta_{42}$ ($P = 0.002$) than HO subjects (Fig. 1B), whereas group differences in the $A\beta_{42}/A\beta_{40}$ ratio didn't reach significance.

PSG sleep

Table 3 summarizes sleep/wake results in the study population. Briefly, REM sleep was significantly shortened ($P = 0.03$) and SWS was more disrupted ($P = 10^{-5}$) in aMCI than in HO subjects (Fig. 1A).

Table 1
Demographic and cognitive profile of the study population.

	HO	aMCI	*P*
Age, yr	67 ± 5.5	69.8 ± 6.5	0.1
Gender (F/M)	10/11	6/15	0.2
Education, yr	8.6 ± 4.3	8.2 ± 5.4	0.8
CDR (sum of boxes)	0	0.5	N/A
MMSE	28.3 ± 1.3	26.7 ± 2.5	0.01*
Immediate recall	14.2 ± 2.9	9.3 ± 2.8	3×10^{-6}*
Delayed recall	13.3 ± 2.7	6.5 ± 4	5×10^{-9}*

Results are expressed as mean ± standard deviation. F/M (female/male). CDR: Clinical Dementia Rating; CDR = 0: no dementia; CDR = 0.5: questionable or very mild dementia; MMSE: Mini-Mental State Examination (0-30); N/A: not applicable.

Table 2
Plasma Aβ levels of the study population.

Aβ marker	HO	aMCI	*P*
$Aβ_{40}$ (pg/ml)	36.4 ± 3.9	56.6 ± 5.5	$6 \times 10^{-3*}$
$Aβ_{42}$ (pg/ml)	4 ± 0.3	6.1 ± 0.4	$2 \times 10^{-3*}$
$Aβ_{42}/Aβ_{40}$	0.23 ± 0.08	0.12 ± 0.08	0.2

Results are expressed as mean ± standard error of the mean. **Post hoc* after significant MANCOVA, adjusted for age and gender.

Subjective levels of daytime sleepiness were not statistically different between the two groups (Table 3), ESS scores were below the cut off for suspecting sleep disorders associated with excessive daytime sleepiness in all participants, and they were not significantly correlated with either cognitive or sleep/wake variables considered in the present study.

Relationships between disturbed sleep physiology and plasma Aβ levels

Evidence suggests that Aβ deposits are associated with sleep deficits in APP-PS1 mice (Roh et al., 2012). To test if this relationship can be extended to different aging trajectories in humans, we investigated whether impaired sleep patterns (i.e., decreased REM and increased SWS fragmentation) correlated with plasma Aβ levels in HO and aMCI subjects. Regression analyses showed positive correlations between density of SWS arousals and levels of $Aβ_{42}$ in aMCI ($F_{(3,20)} = 3.8$, $P = 0.03$; r = 0.57, $P = 0.02$), but not in HO subjects (Fig. 1C). Significant group differences in the relationship between these two factors were further confirmed by comparing regression coefficients

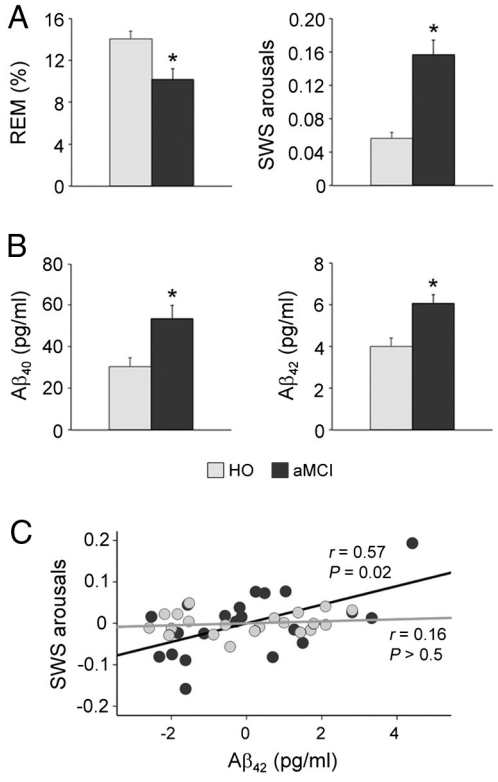

Fig. 1. Sleep disturbances and plasma Aβ levels in aMCI subjects. A. Significant differences in physiological sleep between HO and aMCI subjects. Arousal density in slow-wave sleep (SWS, stage 3 + 4) was determined by dividing the number of arousals in SWS by the time (in hours) spent in SWS. REM: rapid-eye movement sleep. B. Significant differences in plasma Aβ levels between HO and aMCI subjects. C. Regression plot displaying correlations between SWS arousals and plasma $Aβ_{42}$ levels in HO (light grey circles) and aMCI subjects (dark grey circles). All statistical analyses were adjusted for age and gender.

Table 3
Sleep/wake patterns of the study population.

	HO	aMCI	*P*
Sleep parameters			
TST (min.)	395.7 ± 30.7	372.6 ± 55.5	0.2
Sleep latency	11.7 ± 7.4	15 ± 7.1	0.1
Stage 2 (%)	34.6 ± 6.9	36.3 ± 9.3	0.3
SWS (%)	23.6 ± 7	22.7 ± 12.2	0.8
REM (%)	14.1 ± 3.4	10.1 ± 4.6	0.03*
Sleep efficiency (%)	83.8 ± 6.1	78.6 ± 11.5	0.3
Wake parameters			
WASO (%)	13.2 ± 5.8	15.6 ± 6.2	0.5
AI Stage 2	0.31 ± 0.17	0.25 ± 0.13	0.1
AI SWS	0.05 ± 0.03	0.15 ± 0.08	$2 \times 10^{-5*}$
AI REM	0.18 ± 0.14	0.22 ± 0.09	0.2
Daytime sleepiness			
ESS	5.2 ± 2.4	5.6 ± 3.5	0.6

Results are expressed as mean ± standard deviation. TST: total sleep time; WASO: wake after sleep onset; SWS: slow-wave sleep; REM: rapid-eye movement sleep; AI: arousal index. **Post hoc* after significant MANCOVA, adjusted for age and gender.

($P = 0.002$). No significant relationship was found between other plasma Aβ markers and sleep changes neither in aMCI nor in HO subjects.

Group differences in cortical thickness

Group differences in cortical thickness were assessed for the original sample (21 subjects per group; HO: mean age ± SD = 67 ± 5.5 yr; aMCI: mean age ± SD = 69.8 ± 6.5 yr, t-Student $P = 0.1$; HO: 11 males and 10 females; HO: 15 males and 6 females), and for a smaller sample (16 subjects per group) matched in age (HO: mean ± SD = 68.8 ± 5.1 yr; aMCI: mean ± SD = 69 ± 5.2 yr; t-Student $P = 0.9$) and gender (10 males and 6 females in each group).

Results obtained with the original sample (N = 42 subjects) showed a significant thinning of the right precuneus (Fig. SM1, left panel) in aMCI subjects (corrected $P < 0.0001$; cluster size = 191 mm^2), which was confirmed in the age-gender matched sample (N = 32 subjects) (uncorrected $P < 0.0005$; cluster size = 162 mm^2) and extended to posterior cingulate (uncorrected $P < 0.002$; cluster size = 58 mm^2), anterior cingulate (uncorrected $P < 0.002$; cluster size = 52 mm^2), and orbitofrontal cortex (uncorrected $P < 0.003$; cluster size = 100 mm^2) (Fig. SM1, right panel).

Relationships between disturbed sleep physiology and cortical integrity

We next examined if sleep deficits were associated with specific patterns of cortical thinning in each group. Shortened REM sleep in aMCI was significantly correlated with cortical thinning in the left posterior cingulate (corrected $P = 3 \times 10^{-5}$), left precuneus (corrected $P = 4 \times 10^{-4}$), and bilateral postcentral gyri (left: corrected $P = 2 \times 10^{-4}$; right: corrected $P = 9 \times 10^{-7}$). These results are displayed in Fig. 2A together with atlas-based cytoarchitectonic delimitation of significant regions on cortical flattened surfaces (Fig. 2B). No significant relationship between REM sleep and cortical thickness was found in HO subjects. Table 4 includes additional information on significant correlations between reduced REM sleep and cortical thinning in aMCI subjects.

When plasma levels of $Aβ_{40}$ and $Aβ_{42}$ were added to the general linear model, most of the above significant correlations failed to reach significance. In order to assess whether these findings stemmed from a reduction of statistical power, correlation analyses were restricted to regions in which REM sleep showed significant correlations with cortical thickness. Most of correlations survived this analysis, except for those performed with the precuneus, although significances were restricted to smaller areas [27 mm^2 for left posterior cingulate and postcentral gyrus after adding $Aβ_{40}$ as nuisance factor (r = 0.68;

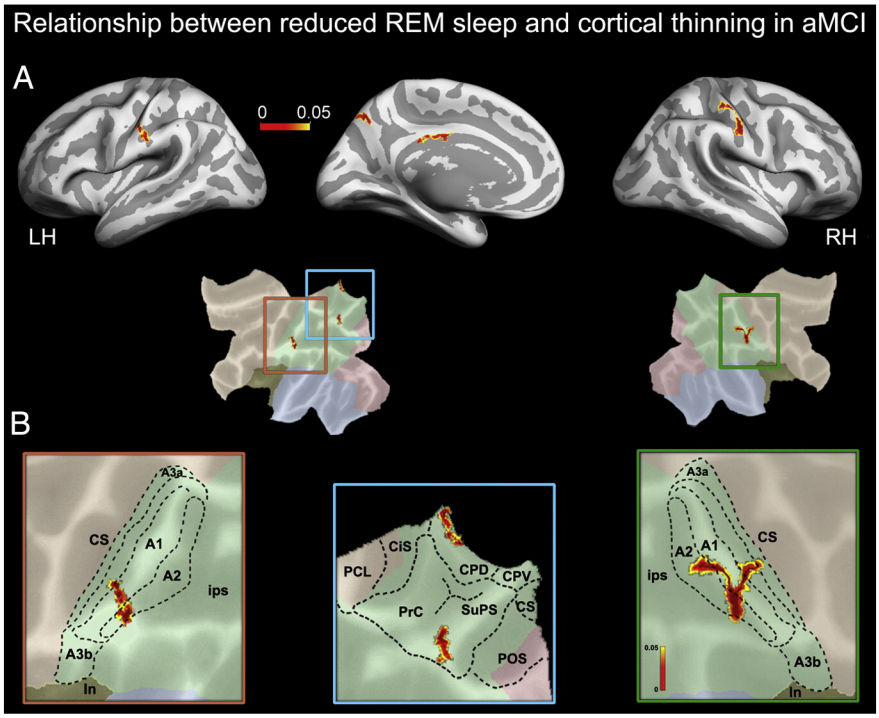

Fig. 2. Relationship between decreased REM sleep and cortical thinning in aMCI subjects. A. Sites of significant correlations between cortical thinning and decreased REM sleep in aMCI subjects, after adjusting for age, gender and normalized mean cortical thickness (corrected for multiple comparisons, $P < 0.05$; cluster extend threshold >90 vertices). LH: left hemisphere; RH: right hemisphere. B. Representation of significant clusters on flattened cortical surfaces derived from human cytoarchitectonic maps of the affected regions. Abbreviations for the primary somatosensory cortex (Greyer et al., 1999): A1, A2, A3a, A3b – Area 1, Area 2, Area 3a, Area 3b of primary somatosensory cortex; CS – central sulcus; ips – intraparietal sulcus; In – insula. Abbreviations for the superior parietal lobe (Scheperjans et al., 2008): PCL – posterior paracentral lobe; CiS – cingulate sulcus; PrC – precuneus; CPD – cingulate postdorsal; CPV – cingulate postventral; SuPS – subparietal sulcus; CS – central sulcus; POS – parieto-occipital sulcus.

$P = 5 \times 10^{-5}$); 54 mm^2 for left posterior cingulate (r = 0.67; $P = 8 \times 10^{-5}$) and 85 mm^2 for left postcentral gyrus (r = 0.48; $P = 0.002$) after adding $A\beta_{42}$ as nuisance factor]. These findings suggest that plasma Aβ levels mediate the relationship between REM sleep and thinning of precuneus in aMCI subjects.

The density of arousals during SWS was not significantly related to cortical thinning neither in HO nor in aMCI subjects, regardless of whether or not plasma Aβ levels were added to the statistical model.

Relationships between plasma Aβ levels and cortical integrity

We further investigated whether changes in plasma Aβ levels correlated with patterns of cortical thinning in each group. These analyses showed that Aβ levels were not significantly related to changes in cortical thickness in HO subjects. However, $A\beta_{40}$ levels were significantly related to thinning of bilateral posterior cingulate cortex (left: corrected $P = 10^{-5}$; right: corrected $P = 4 \times 10^{-5}$) in aMCI subjects (Figs. 3A and B, left panel). In line with the lack of relationship between density of SWS arousals and cortical thickness in aMCI, adding SWS arousals as nuisance variable to the statistical model had no effect on results (left: corrected $P = 6 \times 10^{-5}$; right: corrected $P = 9 \times 10^{-5}$). On the contrary, correlations between increased $A\beta_{40}$ levels and thinning of bilateral posterior cingulate cortex failed to reach significance when REM sleep was added to the statistical model. In principle, this result matches our expectations because both $A\beta_{40}$ levels and REM duration correlated with cortical thinning in the left posterior cingulate. However, a closer look at results illustrated in Figs. 2 and 3 reveals that affected areas of the left posterior cingulate were slightly different in each particular case. Correlation with REM sleep was more evident in BA23 (Table 4) whereas correlation with $A\beta_{40}$ levels reached its maximum in BA31 (Table 5). When regression analyses were limited to these particular regions adding either REM duration or $A\beta_{40}$ levels as nuisance variables, the original correlations survived this analysis although results were restricted to a smaller area (REM as nuisance: 41 mm^2; r = 0.55; $P = 5 \times 10^{-3}$; $A\beta_{40}$ as nuisance: 27 mm^2; r = 0.68; $P = 5 \times 10^{-6}$).

Results further revealed that increased $A\beta_{42}$ levels were significantly associated with thinning of the right entorhinal cortex (corrected $P = 3 \times 10^{-5}$) in aMCI subjects (Figs. 3A and B, right panel). This relationship remained intact after adding density of SWS arousals to the statistical model but vanished after introducing REM sleep as nuisance variable. The latter was unexpected because REM duration was neither related to $A\beta_{42}$ levels nor to thinning of the right entorhinal cortex. To better understand this result, we limited the regression analysis to this region with REM as nuisance factor. The lack of relationship between $A\beta_{42}$ levels and cortical thinning was confirmed; suggesting that reduced REM sleep influenced the strength of association between levels of $A\beta_{42}$ and GM in the right entorhinal cortex of aMCI subjects.

Table 4
Relationship between reduced REM sleep and cortical thinning in aMCI subjects.

Cortical region (BA)	Hemisphere	CS (mm^2)	*P*	*T*	*r*
Postcentral gyrus (BA3)	R	420	9×10^{-7}	4.3	0.56
Postcentral gyrus (BA3)	L	176	2×10^{-4}	4.3	0.56
Precuneus (BA7)	L	133	4×10^{-4}	4.1	0.54
Posterior cingulate (BA23)	L	76	3×10^{-5}	5	0.6

BA: Brodmann area; L: Left; R: Right; CS: cluster size; *P*: corrected *P*-value for the cluster; *T*: t statistic for the cluster. r: correlation value.

Discussion

Evidence suggests that Aβ levels are modulated by the sleep-wake cycle in mice and humans, peaks occurring in periods of greatest physical activity and valleys coinciding with sleep (Bateman et al., 2007; Huang et al., 2012; Kang et al., 2009). Understanding relationships between Aβ levels and sleep might have deep implications for the slowing of AD progression, given that sleep disturbances are considered among

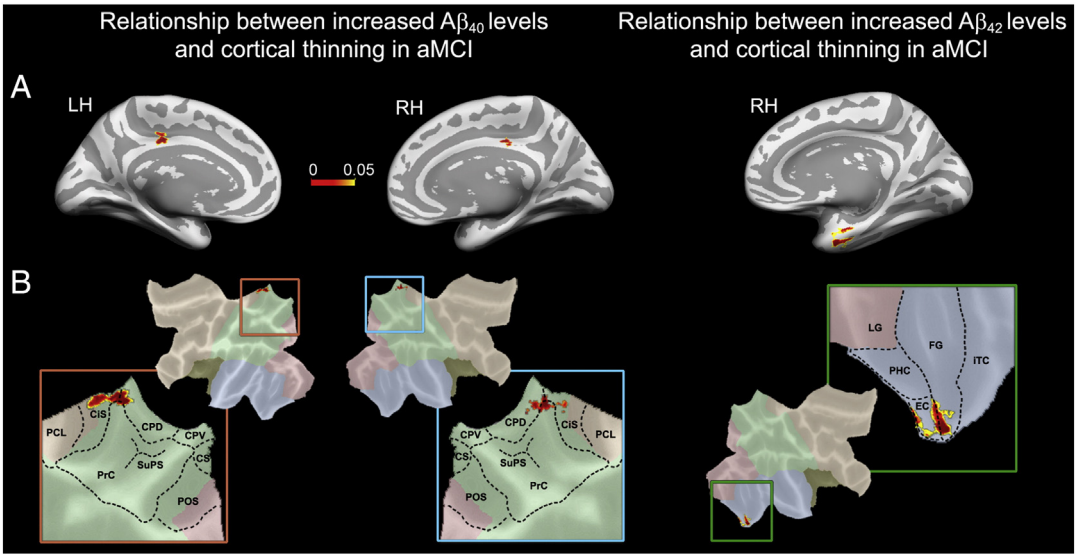

Fig. 3. Relationship between increased plasma Aβ levels and cortical thinning in aMCI subjects. A. Sites of significant correlations between cortical thinning and decreased REM sleep in aMCI subjects, after adjusting for age, gender and normalized mean cortical thickness (corrected for multiple comparisons, $P < 0.05$; cluster extend threshold >90 vertices). LH: left hemisphere; RH: right hemisphere. B. Representation of significant clusters on flattened cortical surfaces derived from human cytoarchitectonic maps of the affected regions. Abbreviations for the superior parietal lobe (Scheperjans et al., 2008): PCL – posterior paracentral lobe; CiS – cingulate sulcus; PrC – precuneus; CPD – cingulate postdorsal; CPV – cingulate postventral; SuPS – subparietal sulcus; CS – central sulcus; POS – parieto-occipital sulcus. Abbreviations for the entorhinal cortex (McDonald et al., 2000): EC – entorhinal cortex; PHC – parahippocampal cortex; FG – fusiform gyrus; iTC – inferior-temporal cortex; LG – lingual gyrus.

the most troubling symptoms of AD (Loewenstein et al., 1982; Prinz et al., 1982; Vitiello et al., 1990). A first look at the association between the presence of Aβ aggregates and sleep has revealed that sleep deficits occur after plaque formation in a mouse model of AD amyloidosis (Roh et al., 2012). Our study extends these findings to aMCI subjects, and provides precise cortical correlates of the link between plasma Aβ levels and sleep disturbances in this population at AD risk.

Linking plasma Aβ levels to impaired sleep in aMCI subjects

Accumulated evidence suggests that the MCI status results from a constellation of pathologic, molecular and cellular mechanisms, in which Aβ pathology plays a central role (Hardy and Selkoe, 2002). Accordingly, *postmortem* studies have established that density of neuritic plaques in neocortex and hippocampus is greater in MCI subjects than in older adults cognitively intact, and considerably less in MCI than in AD patients (Haroutunian et al., 1998). This result has been further confirmed by prospective studies showing that accumulation of Aβ plaques in different neocortical regions strongly correlates with impaired cognitive function along the MCI-AD continuum (Sabbagh et al., 2010). Given that the pathogenic constituent of cerebral amyloid plaques are the Aβ$_{40}$ and Aβ$_{42}$ isoforms, it is not surprising to find enhanced Aβ levels in the brain of MCI subjects. The latter has been extensively corroborated with [(11)C]Pittsburgh Compound B (PiB)-positron emission tomography (PET) scans, showing that patterns of PiB retention in MCI largely resemble that observed in AD patients (Forsberg et al., 2008; Kemppainen et al., 2007). Furthermore, PiB levels in the temporal cortex have demonstrated accounting for episodic memory deficits in MCI subjects (Chetelat et al., 2011).

The current study reveals that increased plasma levels of Aβ$_{42}$ parallels higher SWS fragmentation in aMCI subjects. Mechanisms by which Aβ-related brain pathology is associated with sleep disruptions have started to be unveiled. Mutual interactions between Aβ-induced endoplasmic reticulum (ER) stress and sleep fragmentation could provide a plausible explanation for this relationship. Aβ deposition triggers the unfolded protein response (Chafekar et al., 2008; Nishitsuji et al., 2009; Takahashi et al., 2009; Umeda et al., 2011), a cellular stress response leading to perturbed calcium homeostasis, increased protein accumulation, loss of ER function, and activation of apoptotic cascades when the ER stress response is persistent (Kim et al., 2008; Walter and Ron, 2011). Sleep loss and sleep fragmentation have also demonstrated exacerbation of the ER stress (Naidoo, 2012) together with aging (Naidoo et al., 2008). Therefore, the combination of fragmented SWS and high Aβ load may boost inadequate ER stress responses in early stages of neurodegeneration, and ultimately pave the way for AD.

Our results do not clarify whether higher plasma Aβ levels lead to sleep loss or *vice versa*. Different lines of evidence support the two possibilities. First, it has recently been found that Aβ aggregates induce neural damage that, in turn, leads to impaired sleep in APP-PS1 mice. This damage was attributed to a loss of metabolic coupling between lactate and diurnal Aβ oscillations impeding Aβ clearance by astrocytes and causing synaptic failures due to neurotoxic effects of glutamate accumulation (Roh et al., 2012). Second, HO subjects under conditions resulting in poor sleep quality, like sleep-disordered breathing (Yaffe et al., 2011) and circadian disturbances (Tranah et al., 2011), have shown increased risk to developing MCI or dementia. And these sleep disturbances are intensified with severity of AD (Moe et al., 1995).

However, mechanisms by which disrupted sleep could exacerbate Aβ-related pathology remain unknown to date. One potential explanation comes from aging-related dysfunctions of the hypothalamic-orexin

Table 5
Relationships between increased plasma Aβ levels and cortical thinning in aMCI subjects.

Cortical region (BA)	Hemisphere	CS (mm^2)	*P*	*T*	*r*
Aβ$_{40}$					
Posterior cingulate (BA31)	L	144	10^{-5}	5.5	0.66
	R	58	4×10^{-5}	4.9	0.61
Aβ$_{42}$					
Entorhinal cortex (BA28)	R	282	3×10^{-5}	5	0.62
Aβ$_{40}$ (SWS as nuisance factor)					
Posterior cingulate (BA31)	L	188	6×10^{-5}	4.5	0.58
	R	116	9×10^{-5}	4.7	0.6
Aβ$_{42}$ (SWS as nuisance factor)					
Entorhinal cortex (BA28)	R	177	4×10^{-4}	2.3	0.34

Aβ: amyloid-beta; BA: Brodmann area; SWS: slow-wave sleep; L: Left; R: Right; CS: cluster size; *P*: corrected *P*-value for the cluster; *T*: t statistic for the cluster. *r*: correlation value.

system. Endogenous orexins are involved in maintaining wakefulness (Saper et al., 2005) and also participate in the regulation of diurnal oscillations of extracellular Aβ (Kang et al., 2009). Thus, sleep loss and orexin infusion have shown to disrupt the diurnal rhythm of Aβ oscillation, leading to increased Aβ burden. Both scenarios were reversed with the infusion of a dual orexin receptor antagonist (Kang et al., 2009). Interestingly, overexpression of orexin in transgenic mice resulted in reduction of REM sleep and non-REM sleep fragmentation (Makela et al., 2010; Mieda et al., 2004), the two sleep markers featuring aMCI (Hita-Yañez et al., 2012). Finally, aging-related sleep-wake instability produced increased ER stress and ER dyshomeostasis in orexinergic and noradrenergic wake neurons (Naidoo et al., 2011). Therefore, aging, high Aβ levels and poor sleep quality are elements that in combination may trigger a positive feedback loop that would ultimately facilitate the progression of AD.

Relationship between impaired sleep and cortical loss in aMCI subjects

We found that reduced REM sleep in aMCI subjects was significantly associated with thinning of the bilateral postcentral gyrus, left posterior cingulate, and left precuneus. Although the two first associations were maintained when $A\beta_{40}$ and $A\beta_{42}$ concentrations were added to the statistical model, correlation with the left precuneus was missed. Accordingly, the strength of the association between REM duration and cortical loss in aMCI is largely independent of plasma Aβ levels in the postcentral gyrus and posterior cingulate, but partially dependent on Aβ levels in the left precuneus. Involved regions are of particular interest because they have shown GM loss in early stages of AD, as confirmed in the current study. Thus, aMCI subjects showed thinning of precuneus (corrected results) that was extended to anterior and posterior cingulate cortex (uncorrected results) when both groups were matched in age-gender (Fig. SM1).

Additional studies have revealed significant atrophy of the posterior cingulate cortex in MCI subjects (Chetelat et al., 2002), even in the absence of damage in the anterior cingulate cortex, suggesting that it is not merely a marker of global cortical atrophy associated with incipient neurodegeneration (Pengas et al., 2010). Regarding the precuneus, evidence suggests that this region is more vulnerable to the accumulation of Aβ plaques during the course of disease (Driscoll et al., 2012; Rowe et al., 2007), which may account for its atrophy (Apostolova et al., 2007; Spulber et al., 2012; see also group differences in cortical thickness showed in the Supplementary Material 1) and significant hypometabolism in MCI subjects (Morbelli et al., 2010), as well as for the relationship between increased plasma Aβ levels and cortical thinning observed in the present study. The precuneus also suffers from connectivity disruptions in non-demented older individuals with increased amyloid burden, pointing to a particular susceptibility of this cortical area to early neurodegeneration and functional disconnection in MCI subjects (Drzezga et al., 2011). Finally, cortical thinning of the postcentral gyrus has recently been associated with APOE-ε4 and microtubule-associated protein tau (MAPT-H1) genetic variants in older adults with aMCI (Goñi et al., 2013), and has been further correlated with aberrant patterns of thalamic functional connectivity in MCI and AD patients (Zhou et al., 2013). Both genetic susceptibility and disrupted connectivity suggest that the loss of integrity of the postcentral gyrus might also signal early stages of neurodegeneration.

Shortening of REM sleep observed in aMCI subjects may arise in response to the vulnerability of brainstem neurons involved in REM sleep generation to AD pathology. Accordingly, neurons of the pedunculopontine and laterodorsal tegmentum, essential for the generation of REM sleep, have shown morphological changes in AD brains (Giess and Schlote, 1995; Mufson et al., 1988; Terry and Katzman, 1983). These neurons send cholinergic projections to the nucleus basalis of Meynert (Thakkar et al., 1996; Webster and Jones, 1988), considered as the major source of cholinergic innervation for the entire cortical mantle (Mesulam and Geula, 1988). The basal forebrain cholinergic territories and their cortical projections not only are significantly affected in AD patients (Arendt et al., 1985; McGeer et al., 1984; Teipel et al., 2011; Vogels et al., 1990; Whitehouse et al., 1981), but also have shown decreased volume in aMCI subjects that was further associated with impaired recall (Grothe et al., 2010). Therefore, it might happen that REM deficits observed in aMCI could indicate the level of AD pathology in the basal forebrain cholinergic system, decreasing the number of cholinergic fibers to targeted cortical regions, which in turn could result in loss of cortical function and anatomical integrity.

In agreement with this hypothesis, the posterior cingulate and the precuneus are both targets of a progressive reduction in cortical acetylcholinesterase-rich fibers from normal aging to AD (Geula and Mesulam, 1989) and of the widest range of AD lesions (Brun and Englund, 1981). Furthermore, nicotinic cholinergic binding has been shown to be significantly reduced both in the nucleus basalis of Meynert (Araujo et al., 1988; Shimohama et al., 1986) and in the postcentral gyrus (London et al., 1989) of AD patients, providing a plausible explanation for the relationship between thinning of postcentral gyrus and shortened REM sleep in aMCI subjects.

Associations between plasma Aβ levels and cortical loss in aMCI subjects

Aberrant APP metabolism leading to aggregation of soluble $A\beta_{40}$ and $A\beta_{42}$ oligomers has largely been considered the primary trigger for the development of AD (Selkoe, 1994). Previous studies have assessed relationships between CSF $A\beta_{42}$ levels and GM atrophy in MCI subjects (Desikan et al., 2010; Fjell et al., 2010; Herukka et al., 2008; Vemuri et al., 2009), although only one of these studies used aMCI (Vemuri et al., 2009) whereas none of them combined plasma $A\beta_{42}$ levels with cortical thickness in the same study. Here, we found in aMCI subjects that increased plasma levels of $A\beta_{40}$ and $A\beta_{42}$ were related to thinning of posterior cingulate and entorhinal cortex, respectively; both structures considered canonical AD regions. While the former relationship was independent of sleep deficits, the latter vanished when REM duration was added to the statistical model. The influence of REM sleep on thinning of the right entorhinal cortex was later confirmed, when the regression analysis was limited to this region.

In line with these findings, previous evidence has shown that insoluble $A\beta_{42}$ extracted from entorhinal cortex is correlated with density of neuritic plaques as well as with the Braak stage (Forman et al., 2007). Furthermore, MCI subjects have shown fewer neurons in the entorhinal cortex than HO subjects, decreasing the number of neurons in layer II by 60% and in layer IV by 40% (Gomez-Isla et al., 1996). Our study further showed that decreased REM sleep significantly contributed to correlations between $A\beta_{42}$ levels and thinning of the entorhinal cortex in aMCI subjects, suggesting that both REM deficits and elevated plasma $A\beta_{42}$ levels might signal incipient damage of the entorhinal cortex in older adults at risk for AD. This finding strengthens the hypothesis that REM loss might facilitate and/or accompany lesions of canonical AD regions involved in early neurodegeneration. Furthermore, recent evidence suggests that sleep improves Aβ clearance (Xie et al., 2013), a biological function that might be significantly altered in aMCI subjects due to the presence of sleep disturbances (Geda et al., 2004; Hita-Yañez et al., 2012; Lee et al., 2008; Westerberg et al., 2012). Thus, sleep deficits might lead to accumulation of Aβ oligomers and amyloid depositions, as a consequence of failures in the mechanisms to remove these neurotoxic products that accumulate in the brain during wakefulness (Bateman et al., 2007; Huang et al., 2012; Kang et al., 2009).

Although originally unexpected, we also found significant correlations between plasma $A\beta_{40}$ levels and thinning of the posterior cingulate. This finding might indicate that highly amyloidogenic Aβ species, such as $A\beta_{42}$, are not necessarily more neurotoxic than a less or non-amyloidogenic Aβ specie, such as $A\beta_{40}$.

Whether plasma Aβ levels are useful markers of brain amyloidosis remains controversial to date (Hampel et al., 2011; Koyama et al.,

2012; Rissman et al., 2012; Takeda et al., 2010). While some studies have found correlations between plasma Aβ levels and dementia risk and/or disease progression (Mayeux et al., 2003; Schupf et al., 2008; van Oijen et al., 2006), such findings are largely inconsistent (Fukumoto et al., 2003; Hansson et al., 2010; Roher et al., 2009). Our study confirms that plasma $A\beta_{40}$ levels (van Oijen et al., 2006) and $A\beta_{42}$ (Mayeux et al., 2003; Schupf et al., 2008) are significantly higher in aMCI than in HO subjects. However, we failed to establish group differences in the $A\beta_{42}/A\beta_{40}$ ratio, despite this ratio showed a better diagnostic performance when compared with plasma $A\beta_{42}$ alone (Fei et al., 2011). Although the lack of significant results with the Aβ ratio could be due to the small sample and/or the possible heterogeneity of our aMCI sample, it could also be linked to the cross-sectional nature of our study design. The latter explanation is supported by previous evidence showing that the $A\beta_{42}/A\beta_{40}$ ratio was helpful in identifying cognitively normal subjects who were at increased risk of developing either MCI or AD (Graff-Radford et al., 2007).

Study limitations

This study has several limitations that need mentioning. Firstly, evidence suggests that sleep respiratory breathing disorders appear more frequently in MCI than in HO subjects (Bombois et al., 2010). Furthermore, sleep respiratory abnormalities have been observed in 50% of the subjects older than 65 years even in the absence of obstructive sleep apnea syndrome symptoms (Pavlova et al., 2008). Although we were unable to exclude the presence of sleep respiratory breathing disorders in our aMCI sample on the basis of conventional PSG recordings, it might be valuable to mention that all participants and their bed partners reported no related complaints or previous history of these disorders during the neurologic exploration. Furthermore, subjective levels of daytime sleepiness didn't differ between HO and aMCI subjects, individual ESS scorings were in all cases below the cut off for suspecting sleep disorders associated with excessive daytime sleepiness, and they were unrelated to either cognitive or sleep/wake variables assessed in our study. Nevertheless, further PSG studies including polygraphic respiratory measures are needed to determine whether altered sleep patterns and reductions in GM reported in aMCI subjects have a neurodegenerative basis or, in contrast, are due to exacerbated sleep respiratory breathing disorders (Canessa et al., 2011; Macey et al., 2002).

Secondly, the sample size employed in this study was small and lacked *in vivo* markers of AD pathology (i.e., CSF Aβ-tau and/or amyloid-PET). Further research with larger populations including the above markers is required to increase the generalizability of our results and to put them in context of AD.

Finally, significant relationships between sleep parameters and cortical thickness were based on vertex-wise statistical analyses implemented in general linear models. Therefore, conclusions were mainly grounded in correlations, impeding us to establish a causal relationship between the different markers evaluated. For a better understanding of interactions between plasma Aβ levels, sleep disturbances and loss of cortical integrity in early stages of neurodegeneration, future investigations should be aimed at determining the direction of influence between these markers by modelling interactions between them.

Conclusions

The present study shows that increased plasma $A\beta_{42}$ levels are significantly associated with fragmented SWS in aMCI subjects, suggesting that sleep disruptions may signal Aβ burden in persons at increased risk for AD. We further showed that both reduced REM sleep and plasma Aβ levels in aMCI subjects were significantly related to thinning of cortical regions targeted by AD neuropathology. Collectively, these results provide a preliminary link between altered sleep physiology, increased plasma Aβ levels and cortical thinning in older adults with aMCI. Future research with larger cohorts including CSF and/or PET-amyloid imaging markers is required to confirm that associations reported in the present study are reflective of cerebral Aβ pathology featuring early neurodegeneration.

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